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Review and Meta-analysis

The Role of 18F-FDG-PET/CT Scan in the Management of Multiple Myeloma

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Bone lesion is a myeloma-defining event which is reported in 80% of multiple myeloma patients. Imaging of bone is essential in the evaluation of pattern and extent of bone involvement. Recently, whole body X ray (WBXR) has been replaced by more accurate imaging such as whole bode MRI and FDG-PET/CT scan. This review article provides the advantages and role of PET/CT scan in the diagnosis and management of multiple myeloma patients. Generally, PET/CT in diagnosis of bone involvement of newly diagnosed myeloma patients is more sensitive than WBXR. The prognostic value of PET/CT in newly diagnosed patients has been described as well. Different studies have demonstrated that several PET parameters such as the number of focal lesions (FL), SUV_{max} and extramedullary disease(EMD) may affect the outcome of multiple myeloma patients. Interstingely, the main role of PET/CT in myeloma patients is treatment response monitoring and to some extent assessment of MRD. PET/CT appears to be superior than MRI in evaluation of response due to its ability in differentiating active lesion from negative one.

Introduction

Infiltration and expansion of malignant monoclonal plasma cells, basically in the bone marrow causes multiple myeloma (MM) [1]. As indicated by the global cancer statistics 2018, MM represented 0.9% of all new malignancies and 1.1% of leading causes of cancer death worldwide in 2018 [2]. According to the global burden of multiple myeloma study, age-standardized incidence and mortality were highest in the Australasian, North American, and Western European regions and lowest in Asia, Oceania, and sub-Saharan Africa [3]. It is a proven fact that multiple myeloma develops from an asymptomatic premalignant condition clinically identified as monoclonal gammopathy of undetermined significance (MGUS) [4-5]. Hypercalcemia, anemia, renal function impairment, and bone lesions are classic CRAB features which are currently established diagnostic criteria for symptomatic MM [6]. Recently, International Myeloma Working Group has revised the criteria of diagnosis of MM and has mentioned the use of computed tomography (CT) scan and positron emission tomography (PET) scanning in addition to skeletal radiography to diagnose lytic bone lesions [7]. The most accepted staging system in patients affected by MM includes the international staging system (ISS) and Durie–Salmon staging system (DSS) [8]. The ISS is an easy risk scoring system that includes two parameters; serum β_2-microglobulin level and serum albumin level. This risk stratification system which is established in 2005, classified MM patients into three prognostic groups with different overall survival [9]. DSS predicts survival on the base of four parameters; M component production rate, hemoglobulin concentration, calcium value and the number of lytic bone lesions on X-ray [10]. Interpretation of bone lesions on X-rays have some limitation, so new Durie-salmon plus staging system was developed in 2006 which integrated new imaging techniques such as whole-body CT scan, magnetic resonance imaging (MRI) and whole-body FDG-PET scanning into anatomic and functional staging [11]. Bone involvement is one of the most frequent presentation of multiple myeloma, observed in about two-thirds of patients at the time of diagnosis and in approximately all patients in the course of their diseases [12]. Therefore imaging could be an essential part of the approach to multiple myeloma for detection of lytic bone lesions and identification of extramedullary disease to demonstrate the need for early treatment [12]. Although plain X-rays have been easily available skeletal surveys for a long time, it has a

major limitation. Osteolytic bone lesions could be only detectable if at least 30% of trabecular bone is lost [13-14]. More sensitive imaging modalities such as CT, MRI, and PET can be used as an alternative to detect lytic bone lesions at the earlier stage of disease efficiently [15]. The European Society of Medical Oncology (ESMO) and European Myeloma Network (EMN) guidelines recommend a whole-body low dose CT scan as a new standard imaging for the detection of osteolytic bone lesions. These guidelines also recommend MRI and FDG-PET/CT scans to provide more details according to their availability [16-17]. In this article, I focus primarily on the role of FDG-PET/CT scan in the diagnosis, staging, therapy assessment and detection of minimal residual disease.

Diagnostic value of FDG-PET CT scan

PET/CT scan by using FDG as a radiotracer can detect the glucose hypermetabolism of medullary and intramedullary lesions and gives properly both morphological and functional information [14-18]. It is widely accepted that whole-body PET/CT and MRI are equal in detecting focal bone lesions at diagnosis, however, MRI is more powerful at detecting diffuse disease and PET/CT is more reliable in detecting extramedullary diseases [19-20-21)]. National Oncologic PET Registry (NOPR) has recently published the impact of PET/CT on intended management of 16 different cancer types which reported the highest frequency of a change in intended treatment in multiple myeloma (48.7%) compared to other types of cancers [22]. A high impact of PET on the management of patients with plasma cell disorder has been also demonstrated in a Canadian retrospective study with a change in the planned approach in more than 2/3 of patients [15]. A significant correlation between 18F-FDG parameters (SUVs and kinetics) and bone marrow plasma cell infiltration was approved in 40 patients with primary symptomatic multiple myeloma by a German study in 2015 [23]. Several studies have illustrated the sensitivity and specificity ranging from 75% to 100% in detecting lytic bone lesions and staging by PET/CT scan [24-25]. In patients with nonsecretory multiple myeloma who do not have any measurable parameters, more sensitive skeletal survey methods like PET/CT scan can assess the stage of the disease [26]. Another condition in which PET/ CT scan continues to be a considerable topic is solitary plasmacytoma, a single bone or soft tissue mass of clonal plasma cell with no or small bone marrow plasmacytosis. A panel of expert European hematologists recommended PET/CT or MRI, at least one of them, as a mandatory imaging modalitiy in a case of solitary plasmacytoma to exclude the presence of additional lesions [27]. The last IMWG guideline also recommends the PET/CT scan for the first evaluation of patients with solitary extramedullary plasmacytoma [1].

The role of PET/CT in the assessment of prognosis

Several studies have shown the prognostic value of PET/CT in patients with smoldering multiple myeloma (SMM) and MM. A prospective study of a cohort of 120 patients with SMM has shown the probability of progression to MM in 2 years is 58% for patients with positive PET/CT versus 33% for PET/CT-negative patients [28]. Siontis et al. also showed that patients with SMM who have positive PET/CT scans are at higher (75%) risk of progression to symptomatic MM within 2 years [29]. These studies support the use of PET/CT scan to identifying the patients with SMM at higher risk of progression to symptomatic MM who are probably candidates for early initiation of treatment. Bartel et al. demonstrated the impact of PET/CT parameters such as the number of focal lesions (FL), presence of extramedullary disease (EMD), and SUV of lesions on the survival outcome of patients affected by MM [30]. Another Italian study has prospectively evaluated the prognostic significance of the same PET/CT parameters in patients with MM. This study revealed that FL≥3, SUV>4.2, and EMD in PET/CT associated with shorter PFS and OS [31]. Volume-based PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been used

to measure the metabolic activity of the tumor. Fonti et al. reviewed retrospectively medical data of 47 patients with newly diagnosed untreated MM and measured MTV, determined by FDG-PET/CT. They demonstrated the value of MTV in the prediction of PFS and OS in myeloma patients [32]. Similarly, another study by McDonald et al. found the useful survival implication of MTV and TLG. They also demonstrated the superiority of these volumetric measurements on the number and SUV of focal lesions in the prediction of OS and PFS [33]. A Chinese study has found the correlation between ki-67 expression and increase in FDG uptake in PET/CT in patients with EMM. They have also shown the prognostic implication of combination of ki-67 expression and SUVmax in PET in EMM patients [34]. In another study, Cengiz et al. reported that there was a significant correlation between bone marrow FDG uptake and percentage of CD38- and CD-138 expressing plasma cell. They also revealed the correlation between FDG uptake and some prognostically relevant laboratory parameters such as β2M and CRP [35]. As well the correlation between SUVmax in bone lesions and clinical parameters related to tumor burden such as high M protein, plasma cell >20% in bone marrow, β2M>3.5mg/dl, hypercalcemia at the onset of disease, and increased LDH was reported by Li et al [36].

Evaluation of treatment response with F-FDG PET/CT

18F-FDG PET/CT is a superior imaging modality to evaluate the response to treatment because it can distinguish between active and inactive lesions [12]. Several studies have demonstrated that post-treatment PET negativity correlates with a significant response to therapy. They have found the correlation between FDG suppression before transplantation and better outcome [30-31]. Caldarrela et al. have confirmed the usefulness of FDG PET/CT in assessing the response to treatment in a systematic review of 10 studies involving 690 patients with multiple myeloma and solitary plasmacytoma. They also found that response to treatment could be shown by FDG-PET earlier than other imaging tools such as MRI and whole-body X-ray [37]. Another retrospective study of 282 patients with MM showed that in patients achieving conventionally complete response (CR), positive PET associated with two times higher risk of progression compared to negative PET [38]. Several studies have compared FDG-PET with whole-body MRI in post-treatment setting to provide information about the persistent disease. They confirmed that MRI may have falsely positive results due to persistent signal abnormalities in non-active lesions. While the unique role of PET/CT in the evaluation of response to treatment has been proved [39-40]. Another study on 19 patients with multiple myeloma has demonstrated that FDG-PET before and after the first cycle of chemotherapy may be helpful to identify the patients who would respond to this chemotherapy [41]. In recent years, modern combination therapies in newly diagnosed MM patients have improved the depth of response and have increased the minimal residual disease negativity [42]. several meta-analysis and reviews have shown that MRD negativity associated with increased OS and PFS [43-44]. Therefore, improving the currently employed assays to detect the MRD may be considered one of the major goals in the management of MM patients. Different studies have evaluated the complementary role of PET/CT to existing methods such as bone marrow techniques, multiparameter flow cytometry (MFC) and next-generation sequencing (NGS). They reported higher OS in MRD-/PET- or MRD+/ PET- patients (4-year OS 94.2 and 100 % respectively) compared to PET+ patients (4-year OS 73.8%) [45].

What are the limitations of the FDG-PET scan?

Although the usefulness of PET/CT in diagnosis, staging and treatment monitoring has been suggested by several studies some reviews have demonstrated the limitations of PET/CT in this issue. Limited availability and higher cost compared to conventional imaging are the major causes of less application of PET/CT in the diagnosis and management of multiple myeloma in some institutes. False-positive results may be observed in different inflammatory conditions (such as thyroiditis, inflammatory bowel disease, and esophagitis), chemotherapy within the past 4 weeks,

and radiotherapy within the past 2-3 months. Patients who received granulocyte colony-stimulating factors (GCSF) recently may show false positive uptake of FDG in the bone marrow [46]. Post-surgical and fracture areas can be other important causes of false-positive results in the FDG-PET scan [21]. False-negative results including hyperglycemia and recent use of high dose glucocorticoids are other limitations of FDG-PET for evaluation of patients with multiple myeloma. Sequestration phenomenon may be a potential pitfall in interpreting the post-therapy FDG-PET in myeloma patients. Heavily bone marrow infiltration by tumoral cells causes sequestration of 18F-FDG tracer in the bone marrow and lower availability of tracer to detect other sites of active disease. Successful treatment of bone marrow infiltration leads to an increase in the metabolic activity of residual disease then misinterpretation of the residual lesions as a progressive disease [47].

In conclusion, this mini-review shows that available evidence on the value of PET/CT in diagnosis, staging, prognosis and response monitoring is promising. PET/CT can detect myeloma bone lesions with a sensitivity higher than WBXR and comparable to MRI. It may also provide significant prognostic information in smoldering myeloma and solitary plasmacytoma. Interestingly, PET/CT could be a useful tool to monitor the treatment response due to its ability to detect the metabolic activity in lesions.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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